REMARKS

Claims 1-58 are in this application. Claims 1-44 have been canceled, and claims 45-58 are pending. Claims 45 and 47-58 are currently subject to a provisional double patenting rejection. Claim 45 is amended to its original wording. Claims 45-58 are currently rejected for allegedly being unpatentable under 35 U.S.C. § 103(a) and for failing to comply with 35 U.S.C. § 112, first paragraph. The Examiner has made this rejection final. Applicants traverse each and every rejection.

In response to the Examiner's statement regarding a lack of English translations of the German priority documents, Applicants enclose herewith the requested English translations.

Double Patenting

Claims 45 and 47-58 of the instant application stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 5, 7-8, 11-17, 43-46 and 48-49 of copending Application No. 10/510,673. In response, applicants hereby submit a Terminal Disclaimer with the present Response. It is submitted that the provisional double patenting rejection is thereby overcome, and should be withdrawn.

Claim rejections – 35 U.S.C. § 112

The Examiner has rejected claims 45-58 under 35 U.S.C. § 112 as failing to comply with the written description requirement. The Examiner has stated that "[w]hile applicant demonstrated a weight ratio of 2:1 using 20 mg of oxycodone to 10 mg of naloxone, nowhere did applicant teach the use of 100 mg of oxycodone to 50 mg of naloxone." While applicants maintain that the explicit disclosure of a preferred weight ratio of 2:1 oxycodone to naloxone (page 16, lines 19-21) and of 50 mg naloxone along with a disclosed range of oxycodone including 100 mg (page 17, lines 1-4) provides a sufficient written description, applicants have amended claim 45 again to recite the ranges of about 1 mg to about 50 mg of naloxone and about 10 mg to about 150 mg of oxycodone, which are recited verbatim in the specification. Since these ranges were not previously rejected by the Examiner under 35 U.S.C. § 112, Applicants submit that the rejection under 35 U.S.C. § 112 is thereby overcome.

Claim rejections – 35 U.S.C. § 103(a)

The Examiner has rejected claims 45-58 under 35 U.S.C. § 103(a) as being unpatentable over PCT Publication No. WO 99/32119 to Kaiko et al. (hereinafter "Kaiko") in view of U.S. Patent No. 3,773,955 to Pachter et al. (hereinafter "Pachter"). Applicants respectfully traverse.

The present invention is directed to providing a controlled release opioid formulation having a 2:1 oxycodone:naloxone ratio which provides effective analgesia and at the same time shows a reduced side effect profile. Submitted as Exhibit A to the January 21, 2009 Response and Amendment was a copy of Clinical Study Results for Controlled Release Oxycodone/Naloxone Formulations ("Clinical Study Results"). The Clinical Study Results reference discusses the results of a Phase II clinical study wherein 202 patients were randomized, of which 152 patients received controlled release oxycodone and controlled release naloxone and 50 patients received controlled release oxycodone and placebo. Among the patients who received oxycodone and naloxone, the ratio of oxycodone:naloxone varied from 1:1 to 8:1. The conclusion drawn from the study was that, if all aspects of treatment are taken into account, *i.e.*, reduction of pain intensity, improvement of bowel function index, occurrence of adverse effect, avoidance of diarrhea, tolerability and preference, the 2:1 oxycodone:naloxone ratio was the best.

The results of that same Phase II clinical study are also discussed in previously submitted Nadstawek et al., Patient Assessment of a Novel Therapeutic Approach for the Treatment of Severe Chronic Pain, Int. J. Clin. Pract. 2008, 62(8):1159-1167 (previously submitted as Exhibit C) and Meissner et al., A Randomized Controlled Trial With Prolonged-Release Oral Oxycodone and Naloxone to Prevent and Reverse Opioid-Induced Constipation, Eur. J. Pain, 2009 Jan.; 13(1):56-64, Epub 2008 Aug. 31 (attached hereto as Exhibit D; previously submitted, also as Exhibit D, as Eur. J. Pain (2008) doi:10.1016/j.ejpain 2008.06.012 while the article was in press).

The foregoing references were based, at least in part, on Mundipharma GmbH Clinical Study Report OXN 2401, June, 2005 (attached as Exhibit E). The content of Clinical Study Report OXN 2401 is also discussed, at least in part, in copending U.S. patent applications serial no. 11/885,285 and 11/885,288, assigned to Euro-Celtique S.A. To the extent that any of the submitted references, Exhibits A-E, or the cited copending applications discuss Bowel Function Index, the method for assessment and/or related data was derived, at

least in part, from the study report entitled Validation of the Bowel Function Index, July 2005 (copy attached as Exhibit F), prepared by United Biosource Corp. for Mundipharma Research GmbH & Co KG ("Mundipharma Research").

Additionally, as discussed in Vondrackova et al., Analgesia Efficacy and Safety of Oxycodone in Combination with Naloxone as Prolonged Release Tablets in Patients With Moderate to Severe Chronic Pain, J. Pain, Dec. 2008, 9(12):1144-1154 (previously submitted as Exhibit B), a Phase III clinical study was performed on a population of 463 patients, comparing controlled release oxycodone/naloxone in a 2:1 ratio with both controlled release oxycodone and placebo. The study concluded that the addition of naloxone to oxycodone in a controlled release tablet in a 2:1 oxycodone to naloxone ratio did not negatively affect the analgesic efficacy of controlled release oxycodone taken alone. Furthermore, the controlled release 2:1 oxycodone:naloxone tablet improved bowel function and opioid tolerability.

Please note that each of the foregoing references, submitted as Exhibits A-F, discuss clinical studies which were designed by Mundipharma Research and/or Mundipharma GmbH and/or conducted by qualified investigators under the sponsorship of Mundipharma Research and/or Mundipharma GmbH. Each of Exhibits A-E was authored, at least in part, by one or more employees of Mundipharma Research and/or Mundipharma GmbH. Euro-Celtique S.A., the assignee of the present invention and the above-cited copending applications, Mundipharma Research and Mundipharma GmbH are associated companies.

Notably, neither Kaiko or Pachter addresses the incorporation of naloxone into an oxycodone dosage form in order to improve the patient's bowel function, let alone the 2:1 oxycodone:naloxone weight ratio in a controlled release matrix as presently claimed.

The presently claimed invention comprises a controlled release dosage form containing oxycodone and naloxone in a 2:1 weight ratio. Kaiko does not teach the 2:1 ratio of oxycodone to naloxone as claimed in the present application, and in fact, Kaiko does not provide any specific ratios for the use of the antagonist naloxone. Kaiko only provides specific ratios for the use of agonists with the antagonist naltrexone. The Final Office Action mailed on June 12, 2009 acknowledges that Kaiko does not teach the limitation of a 2:1 ratio of oxycodone to naloxone (*see*, page 11, lines 1-3 of the June 12, 2009 Office Action).

Kaiko's invention is directed to "an oral dosage form of an opioid analgesic which is subject to less abuse potential via the oral route..." (page 6, lines 10-11). Kaiko contrasts the oral potency of naloxone and naltrexone, stating that naloxone "is absorbed after oral

administration, but has been reported to be metabolized into an inactive form in its first passage through the liver such that it has been reported to be only one fiftieth as potent when parenterally administered" (emphasis added), whereas naltrexone and cyclazocine "retain much of their efficacy by the oral route" (page 13, lines 27-30 and 32-34).

Kaiko discloses and claims a weight ratio of naltrexone:oxycodone of 0.037 to 0.296:1, and a more preferred ratio of 0.056 to 0.222:1. If one multiplies these ratios by a factor of 50 to account for Kaiko's stated poor oral potency of naloxone as compared to naltrexone, the ratio of naloxone:oxycodone would be 1.85 to 14.8:1, and the more preferred range would be 2.8 to 11.1:1. Thus, in contrast to the presently claimed oxycodone:naloxone ratio of 2:1, Kaiko teaches that the ratio should be about 2:3.7 to 2:29.6. It is submitted that for one to rely on Pachter as support for drastically changing Kaiko's oxycodone:naloxone ratio to 2:1 is simply contrary to Kaiko's disclosure and can only be contrived in hindsight based upon the present invention.

However, the Examiner maintains that Pachter would have taught one of skill in the art to use a 2:1 oxycodone:naloxone weight ratio in the controlled release dosage form of Kaiko. It is first noted that Pachter is directly solely to immediate release dosage forms. The present claims require a controlled release dosage form. It is respectfully submitted that the Examiner is picking and choosing only one alleged portion of the Pachter reference, while ignoring the remainder of Pachter's disclosure. For this reason as well, it is submitted that the obviousness rejection is improper. Furthermore, Pachter contrasts the parenteral and oral potency of naloxone as follows:

> However, while naloxone is extremely potent parenterally (a parenteral dose of 0.1 mg. to 2.5 mg will produce narcotic withdrawal symptoms in the addict or have a narcotic reversal effect in an overdose situation), the compound must be administered in quantities 200 to 400 times greater than the parenteral dose to obtain the same effect orally.

(Col. 2, lines 46-52).

There can be no question that Kaiko's formulation and invention explicitly addressed oral abuse of oxycodone, and Pachter's formulation and invention explicitly addressed the parenteral abuse of opioids. Thus, assuming arguendo, that one of skill were to attempt to apply Pachter's teachings to Kaiko's controlled release dosage form directed to preventing oral abuse, the skilled person would have multiplied the naloxone portion of the 2-20:1 oxycodone:naloxone ratio of Pachter by the oral potency factor of 200 to 400 taught by

Pachter. The result is a 2-20:200-400 for the oxycodone:naloxone weight ratio. The present invention requires a 2:1 oxycodone:naloxone weight ratio, a ratio which cannot be arrived at if one were to follow the explicit teachings of Kaiko and Pachter, taken either alone or in the proposed combination.

Moreover, one skilled in the art as of the priority date of the present application would have had no motivation to combine Kaiko and Pachter as these two prior art references clearly address different objectives. Kaiko focused on dosage forms which were less abuse-prone upon oral administration while Pachter specifically addressed immediate release formulations which were less prone to parenteral abuse. Kaiko distinguished its invention from Patcher by stating they were concerned with different problems, *i.e.*, Pachter with parenteral abuse, Kaiko with oral abuse (Kaiko p. 5, lines 10-14).

A review of the stated objects of the respective inventions of Kaiko and Pachter illustrate the stark differences. Kaiko states the following:

> It is an object of the invention to provide an oral dosage form of an opioid analgesic which is subject to less abuse potential via the oral route than prior commercially available dosage forms.
>
> ***
>
> It is a further object of the invention to provide a method of treating pain in human patients with an oral dosage form of an opioid analgesic while reducing the oral abuse potential of dosage form.
>
> It is a further object of the invention to provide a method of manufacturing an oral dosage form of an opioid analgesic such that it has less oral abuse potential.

(page 6, lines 10-12 and 22-26).

In contrast, Pachter states the following:

> The object of the invention was achieved by the formulation of a composition comprising an orally inactive dose of naloxone and an orally active strong, i.e., narcotic or narcotic-like, analgetic agent in oral dosage form which, when administered parenterally, had no drug abuse potential.
>
> It is our invention to combine a parenterally effective but orally ineffective dose of naloxone with an oral analgetic dose of an orally effective strong analgetic without interfering with the analgetic effect of the analgetic upon oral administration. At the same time, however, if any of the oral dosage form should be diverted into the hands of the addict or potential addict, the composition when injected parenterally would not produce any euphoria and in an addict would, in fact, actually cause some withdrawal symptoms.

It is further submitted that one of ordinary skill would not have combined the oxycodone:naloxone weight ratio information of Pachter with the controlled release dosage form of Kaiko, since the references are explicitly directed to disparate types of abuse which require vastly different oxycodone:naloxone weight ratios. However, even assuming arguendo that if one were to make such a combination and follow the teachings of the references, the combination would result in a dosage form having a much higher naloxone content than the 2:1 oxycodone:naloxone ratio required by the claims of the present application.

Lastly, it is respectfully noted that the Examiner misstated that Pachter teaches "an oral active dose of naloxone" (Office Action, page 11). As shown above and stated throughout Pachter, the reference discloses an orally inactive dose of naloxone.

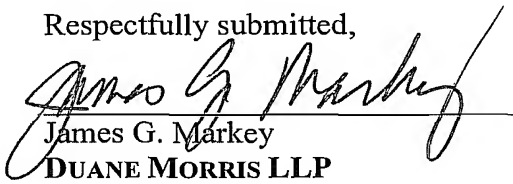
It is also respectfully noted that the Examiner reversed the oxycodone:naloxone ratio taught by Kaiko and substituted naltrexone for naloxone (Office Action, page 3). Kaiko teaches a ratio of 1.85 to 14.8:1 naloxone:oxycodone, which translates into a 2:3.7 to 2:29.6 ratio of oxycodone:naloxone, rather than the 2:1 presently claimed.

Conclusion

Applicants respectfully submit that this response puts the claims of the instant application in condition for allowance, and respectfully request the Examiner to issue a notice of allowance in this application. It is believed that no fee beyond the fees for the Petition for Extension of Time, the Supplemental Information Disclosure Statement, and the Request for Continued Examination is due. However, the Commissioner is hereby authorized to charge any required fees to Duane Morris LLP Deposit Account No. 04-1679.

Respectfully submitted,

Date: October 13, 2009



31,636
James G. Markey (Reg. No.)

DUANE MORRIS LLP
1540 Broadway
New York, NY 10036
Tel. 212-692-1000
Fax. 212-692-1020